CARBON DIOXIDE-ASSISTED METHODS OF PROVIDING BIOCOMPATIBLE INTRALUMINAL PROSTHESES

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/426,126, filed November 14, 2002, the disclosure of which is incorporated herein by reference in its entirety as if set forth fully herein.

FIELD OF THE INVENTION

The present invention relates generally to medical devices and, more particularly, to methods of providing biocompatible medical devices.

BACKGROUND OF THE INVENTION

Stents are typically used as adjuncts to percutaneous transluminal balloon angioplasty procedures, in the treatment of occluded or partially occluded arteries and other blood vessels. As an example of a balloon angioplasty procedure, a guiding catheter or sheath is percutaneously introduced into the cardiovascular system of a patient through the femoral arteries and advanced through the vasculature until the distal end of the guiding catheter is positioned at a point proximal to the lesion site. A guidewire and a dilatation catheter having a balloon on the distal end are introduced through the guiding catheter with the

guidewire sliding within the dilatation catheter. The guidewire is first advanced out of the guiding catheter into the patient's vasculature and is directed across the arterial lesion. The dilatation catheter is subsequently advanced over the previously advanced guidewire until the dilatation balloon is properly positioned across the arterial lesion. Once in position across the lesion, the expandable balloon is inflated to a predetermined size with a radiopaque liquid at relatively high pressure to radially compress the atherosclerotic plaque of the lesion against the inside of the artery wall and thereby dilate the lumen of the artery. The balloon is then deflated to a small profile so that the dilatation catheter can be withdrawn from the patient's vasculature and blood flow resumed through the dilated artery.

Balloon angioplasty sometimes results in short or long term failure (restenosis). That is, vessels may abruptly close shortly after the procedure or restenosis may occur gradually over a period of months thereafter. To counter restenosis following angioplasty, implantable intraluminal prostheses, commonly referred to as stents, are used to achieve long term vessel patency. A stent functions as scaffolding to structurally support the vessel wall and thereby maintain luminal patency, and are transported to a lesion site by means of a delivery catheter.

Types of stents may include balloon expandable stents, spring-like, self-expandable stents, and thermally expandable stents. Balloon expandable stents are delivered by a dilitation catheter and are plastically deformed by an expandable member, such as an inflation balloon, from a small initial diameter to a larger expanded diameter. Self-expanding stents are formed as spring elements which are radially compressible

about a delivery catheter. A compressed self-expanding stent is typically held in the compressed state by a delivery sheath. Upon delivery to a lesion site, the delivery sheath is retracted allowing the stent to expand. Thermally expandable stents are formed from shape memory alloys which have the ability to expand from a small initial diameter to a second larger diameter upon the application of heat to the alloy.

Polymeric materials are increasingly being utilized in intraluminal prostheses, such as stents, as well as in other types of medical devices used within the bodies of subjects. Polymeric materials conventionally utilized in the medical device industry for implantation within the bodies of subjects include, but are not limited to polyurethanes, polyolefins (*e.g.*, polyethylene and polypropylene), poly(meth)acrylates, polyesters (*e.g.*, polyethyleneterephthalate), polyamides, polyvinyl resins, silicon resins (*e.g.*, silicone rubbers and polysiloxanes), polycarbonates, polyfluorocarbon resins, synthetic resins, and polystyrene.

Many conventional polymeric materials contain a range of additives (*e.g.*, plasticizers, antioxidants, UV stabilizers, etc.) as well as a host of contaminants (*e.g.*, residual monomer, oligomers, solvent residues, catalysts, initiators, etc.). For example, casting solvents such as dimethyl sulfoxide (DMSO), chloro-organics, aromatics, tetrahydrofuran (THF), etc. are conventionally utilized in stent production. Moreover, various toxic organic solvents and plasticizers are conventionally used to impregnate the polymeric material of implantable devices, such as intraluminal prostheses, with pharmacological agents. Trace quantities of these materials may remain in the polymeric materials during fabrication of these devices and patients receiving these

devices, or pharmacological agents eluted therefrom, may be exposed to these potentially toxic materials, particularly when the implantable device erodes.

As such, it is desirable to purify polymeric materials utilized in medical devices, such as intraluminal prostheses, in order to remove solvents and other potentially toxic materials and to enhance the biocompatibility of the polymeric material. Unfortunately, conventional purification methods may involve applying heat to the polymeric material. The addition of heat may alter the physical characteristics of the polymeric material, thus negatively affecting the biocompatibility of the material.

SUMMARY OF THE INVENTION

Methods of producing biocompatible intraluminal prostheses according to embodiments of the present invention utilize densified carbon dioxide to remove toxic materials. According to embodiments of the present invention, the polymeric material of an intraluminal prosthesis is immersed in a densified carbon dioxide composition to absorb toxic materials (*e.g.*, organic solvents (polar or non-polar), unpolymerized monomers, polymerization catalysts, and polymerization initiators, etc.) therefrom. The term "toxic materials" includes all types of foreign materials, contaminants, chemicals, physical impurities, and the like, without limitation, that may be harmful to a subject. The densified carbon dioxide composition containing the toxic materials is then removed (completely or partially) from the polymeric material and the toxic materials are easily be separated from the carbon dioxide composition by decreasing the density of the carbon dioxide.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a flowchart of operations for impregnating polymeric material with pharmacological agents, according to embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now is described more fully hereinafter with reference to the accompanying drawings, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The term "biocompatible" as used herein, is intended to denote a material that upon contact with a living element such as a cell or tissue, does not cause toxicity.

The term "dosage regimen" is used herein to describe both exogenously administered and internally administered pharmacological agents. A dosage regimen includes both an amount of a pharmacological agent and time(s) that each dose is to be taken. A dosage regimen may also indicate whether a pharmacological agent is to be taken with food or not, and whether other pharmacological agents are to be avoided.

The term "eluting" is used herein to mean the release of a pharmacological agent from a polymeric material. Eluting may also refer to the release of a material from a substrate via diffusional mechanisms or by release from a polymeric material/substrate as a result of the breakdown or erosion of the

material/substrate.

The term "erodible" as used herein refers to the ability of a material to maintain its structural integrity for a desired period of time, and thereafter gradually undergo any of numerous processes whereby the material substantially loses tensile strength and mass. Examples of such processes comprise enzymatic and non-enzymatic hydrolysis, oxidation, enzymatically-assisted oxidation, and others, thus including bioresorption, dissolution, and mechanical degradation upon interaction with a physiological environment into components that the patient's tissue can absorb, metabolize, respire, and/or excrete. The terms "erodible" and "degradable" are intended to be used herein interchangeably.

The term "hydrophobic" is used herein to mean not soluble in water.

The term "hydrophilic" is used herein to mean soluble in water.

The term "lumen" is used herein to mean any inner open space or cavity of a body passageway.

The terms "polymer" and "polymeric material" are synonymous and are to be broadly construed to include, but not be limited to, homopolymers, copolymers, terpolymers, and the like.

The term "prosthesis" is used herein in a broad sense to denote any type of intraluminal prosthesis or other device which is implanted in the body of a subject for some therapeutic reason or purpose including, but not limited to stents, drug delivery devices, etc.

The term "subject" is used herein to describe both human beings and animals (*e.g.*, mammalian subjects) for medical, veterinary, testing and/or screening purposes.

The term "toxic materials" is intended to

include all types of foreign materials, contaminants, chemicals, physical impurities, and the like, without limitation, that may be harmful to a subject.

As used herein, phrases such as "between X and Y" and "between about X and Y" should be interpreted to include X and Y.

As used herein, phrases such as "between about X and Y" mean "between about X and about Y."

As used herein, phrases such as "from about X to Y" mean "from about X to about Y."

Referring now to **Fig. 1**, methods of producing biocompatible intraluminal prostheses (*e.g.*, stents, etc.), according to embodiments of the present invention are illustrated. Embodiments of the present invention can be employed in conjunction with a number of manufacturing processes associated with producing intraluminal prostheses including, but not limited to, extrusion, pultrusion, injection molding, etc. Moreover, embodiments of the present invention may be utilized in batch, semicontinuous, or continuous processes.

An intraluminal prosthesis (*e.g.*, a stent, drug delivery device, etc.) comprising polymeric material (*e.g.*, formed from polymeric material, or having a partial or complete coating of polymeric material) is provided (Block **100**). The polymeric material may contain trace amounts of one or more toxic materials as a result of previous fabrication steps. For example, residual amounts of various casting solvents including, but not limited to, organic solvents (polar or non-polar) such as DMSO, dimethyl acetimide (DMAc), dimethyl foramide (DMF), chloro-organics, aromatics (such as benzene, toluene, xylene, chlorobenzene), THF, TFF, diglyac glycol, esters, etc. may be present, as would be understood by one skilled in the art. In addition, unpolymerized monomers,

oligomers, polymerization initiators, catalysts, etc. may be present, as would be understood by one skilled in the art. Oligomers are undesired, low molecular weight molecules that may be linear or cyclic.

According to embodiments of the present invention, levels of toxic materials can be reduced to predetermined, acceptable values in parts per million (ppm) based upon specific toxic materials. For example, toxic material "A" that is present in the polymeric material of an intraluminal prosthesis at levels of from greater than 200, 400, 600, 800 or 1,000 ppm, may be reduced to "acceptable" values of, for example, 20, 50, 100, 200, or 400 ppm, etc.

Exemplary polymeric materials that may be utilized in intraluminal prostheses (and in accordance with embodiments of the present invention) include, but are not limited to, polyurethanes, polyolefins, poly(meth)acrylates, polyesters, polyamides, polyvinyl resins, silicon resins, polycarbonates, polyfluorocarbon resins, synthetic resins, and polystyrene. In addition, polymeric material of intraluminal prostheses may be erodible (or an intraluminal prosthesis may have an erodible coating) or non-erodible (or an intraluminal prosthesis may have a non-erodible coating).

Intraluminal prostheses according to embodiments of the present invention, may be formed from various materials. In addition, intraluminal prostheses having polymeric coatings, according to embodiments of the present invention, may be metallic prostheses or polymeric prostheses.

Exemplary erodible materials that may be utilized in intraluminal prostheses (and in accordance with embodiments of the present invention) include, but are not limited to, surgical gut, silk, cotton,

liposomes, poly(hydroxybutyrate), polycarbonates, polyacrylates, polyanhydrides, polyethylene glycol, poly(ortho esters), poly(phosphoesters), polyesters, polyamides (such as polyamides derived from D-glucose), polyphosphazenes, poly(*p*-dioxane), poly(amino acid), polyglactin, and copolymers thereof, erodible hydrogels, natural polymers such as collagen and chitosan, etc. *See, e.g.*, U.S. Patent No. 5,723,508 to Healy et al. Particular examples of suitable erodible polymers include, but are not limited to, aliphatic polyester polymers such as poly(lactic acid), poly(L-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(D-lactic-co-glycolic acid), poly(L-lactic-co-glycolic acid), poly (D,L-lactic-co-glycolic acid), poly(Є-caprolactone), poly(valerolactone), poly(hydroxy butyrate) (including poly(hydroxy butyrate valerate)), poly(hydrovalerate), polydioxanone, poly(propylene fumarate), etc., including copolymers thereof such as polylactic acid-polyethylene glycol block copolymer, and poly(ethyleneoxide)-poly(butylenetetraphthalate), poly(lactic acid-*co*-lysine), poly(Є-caprolactone copolymers), poly(L-lactic acid copolymers), *etc. See, e.g.*, J. Oh et al., PCT Application WO 99/59548 at page 2. Additional examples of erodible polymers are set forth in U.S. Patent No. 5,916,585 to Cook et al. at col. 9 line 53 to col. 10 line 22. The molecular weight (that is, average molecular weight) of the polymer may be from 1,000, 10,000, 100,000 or 500,000 to 2,000,000 or 4,000,000 Daltons, or more. Exemplary non erodible materials that may be utilized in intraluminal prostheses (and in accordance with embodiments of the present invention) include, but are not limited to, fluoropolymers, polyesters, PET, polyethylenes, polypropylenes, etc., and/or ceramics, such as

hydroxyapetite.

Moreover, intraluminal prostheses may include various pharmacological agents. In general, pharmacological agents suitable for inclusion in prosthesis materials and/or coatings (and according to embodiments of the present invention) include, but are not limited to, drugs and other biologically active materials, and may be intended to perform a variety of functions, including, but not limited to: anti-cancer treatment (*e.g.*, Resan), anti-clotting or anti-platelet formation, the prevention of smooth muscle cell growth, migration, proliferation within a vessel wall. Pharmacological agents may include antineoplastics, antimitotics, antiinflammatories, antiplatelets, anticoagulants, antifibrins, antithrombins, antiproliferatives, antibiotics, antioxidants, and antiallergic substances as well as combinations thereof. Examples of antineoplastics and/or antimitotics include paclitaxel (cytostatic and ant-inflammatory) and it's analogs and all compounds in the TAXOL® (Bristol-Myers Squibb Co., Stamford, Conn.) family of pharmaceuticals, docetaxel (*e.g.*, TAXOTERE® from Aventis S. A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (*e.g.*, ADRIAMYCIN® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (*e.g.*, MUTAMYCIN® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of antiinflammatories include Sirolimus and it's analogs (including but not limited to Everolimus and all compounds in the Limus family of pharmaceuticals), glucocorticoids such as dexamethasone, methylprednisolone, hydrocortisone and betamethasone and non-steroidal antiinflammatories such as aspirin, indomethacin and ibuprofen. Examples of antiplatelets,

anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, Mass.) Examples of cytostatic or antiproliferative agents or proliferation inhibitors include everolimus, actinomycin D, as well as derivatives and analogs thereof (manufactured by Sigma-Aldrich, Milwaukee, Wis.; or COSMEGEN® available from Merck & Co., Inc., Whitehouse Station, N.J.), angiopeptin, angiotensin converting enzyme inhibitors such as captopril (*e.g.*, CAPOTEN® and CAPOZIDE® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (*e.g.*, Prinivilo and PRINZIDE® from Merck & Co., Inc., Whitehouse Station, N.J.); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name MEVACOR® from Merck & Co., Inc., Whitehouse Station, N.J.), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents that may be used include alphainterferon, genetically engineered epithelial cells, and dexamethasone.

U.S. Patent Nos. 4,994,033 to Shockey et al.; 5,674,192 to Sahatian et al. and 5,545,208 to Wolff et al. disclose catheters comprising absorbable/ biodegradable polymers or hydrogels containing the desired dosage of a drug. Stents incorporating drug delivery may be found, for example, in U.S. Patent Nos. 5,766,710 to Turnlund et al.; 5,769,883 to Buscemi et al.; 5,605,696 to Eury et al.; 5,500,013 to Buscemi et al.; 5,551,954 to Buscemi et al. and 5,443,458 to Eury, each of which is incorporated herein by reference in its entirety.

Referring back to **Fig. 1**, the polymeric material of an intraluminal prosthesis is immersed in a densified (*e.g.*, liquid or supercritical) carbon dioxide composition for a time sufficient, and under controlled conditions, to cause the trace amounts of toxic materials to be absorbed by the densified carbon dioxide composition (Block **110**). Carbon dioxide is non-toxic, non-flammable, chemically inert, completely recoverable, abundant and inexpensive. Carbon dioxide has properties that are between those of many liquids and gases. At room temperature and above its vapor pressure, carbon dioxide exists as a liquid with a density comparable to organic solvents but with excellent wetting properties and a very low viscosity. Above its critical temperature and pressure (31°C and 73.8 bar), carbon dioxide is in the supercritical state and has gas-like viscosities and liquid-like densities. Small changes in temperature or pressure cause dramatic changes in the density, viscosity, and dielectric properties of supercritical carbon dioxide, making it an unusually tunable, versatile, and selective solvent.

The densified carbon dioxide composition, according to embodiments of the present invention, may be

heterogeneous or homogeneous in composition, *i.e.*, may be a single phase composition or contain one or more additional phases, such as in the form of a microemulsion, emulsion, dispersion, suspension, etc. The densified carbon dioxide composition may comprise, consist of, or consist essentially of carbon dioxide. Where multiple phases are found in the densified carbon dioxide composition, the carbon dioxide may be in the continuous phase.

One or more other ingredients may be included in the densified carbon dioxide composition, such as co-solvents (*i.e.*, water or organic co-solvents such as ethanol and methanol), surfactants or the like may be included. Where one or more organic co-solvents are included, it or they may be polar or nonpolar (or at least one of each). Where one or more surfactants are included it or they may comprise a carbon dioxide-philic group coupled to either a lipophilic or hydrophilic group, a conventional surfactant comprising a liphophilic group coupled to a hydrophilic group, or one or more of each. The densified carbon dioxide composition may comprise at least 30, 40, 50, 60, 70, 80 or 90 percent by weight of carbon dioxide. When water is present in the densified carbon dioxide composition, the water may comprise from about 0.01, 0.1, or 0.5 to about 1, 5, 10 or 20 percent by weight of the composition, or more.

Immersing the polymeric material of the intraluminal prosthesis in the densified carbon dioxide composition under controlled conditions includes, but is not limited to, controlling one or more of the following parameters associated with the densified carbon dioxide composition in a predetermined pattern: temperature, rate of temperature change, pressure, rate of pressure change, composition quantity, etc. Changes in one or more of

these parameters (also referred to as "tuning" the densified carbon dioxide composition) can be made to selectively absorb trace amounts of toxic materials. Moreover, changes in one or more of these parameters can control both the effectiveness and efficiency of toxic material removal.

Referring back to **Fig. 1**, the densified carbon dioxide composition containing the toxic materials is removed from contact with the polymeric material (Block **120**). Removal may include complete removal or partial removal. The density of the removed densified carbon dioxide composition is lowered such that the trace amounts of toxic materials entrained therein become separated therefrom (Block **130**). The separated toxic materials are then disposed of (Block **140**). The density of the removed densified carbon dioxide composition may be lowered by reducing pressure and/or increasing temperature, as would be understood by one skilled in the art.

Embodiments of the present invention described above with respect to **Fig. 1** may be carried out using apparatus known to those skilled in the art. Immersing the polymeric material of an intraluminal prosthesis in a densified carbon dioxide composition for a time sufficient (Block **110**) may be performed within an enclosed chamber (*e.g.*, pressure vessel). Lowering the density of the densified carbon dioxide composition (Block **130**) may also be performed within an enclosed chamber, for example an enclosed chamber separate from a chamber within which the polymeric material is immersed in the densified carbon dioxide composition.

According to embodiments of the present invention, selective removal of toxic or other materials may be accomplished via any of a variety of known masking

techniques. For example, a mask may be applied to one or more portions of an intraluminal prosthesis such that toxic materials are removed only from non-masked portions of the polymeric material. Masking techniques are well understood by those skilled in the art and need not be described further herein.

Intraluminal prostheses provided in accordance with embodiments of the present invention may be employed in sites of the body other than the vasculature including, but not limited to, biliary tree, esophagus, bowels, tracheo-bronchial tree, urinary tract, etc.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.